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| TAFT, STETTINIUS & HOLLISTER LLP SUITE 1800 425 WALNUT STREET CINCINNATI, OH 45202-3957 | | | CHEN, SHIN LIN | |
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| | | | 1632 | |

DATE MAILED: 10/06/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.

10/798,037

Applicant(s)

ROBBINS, JEFFREY

Examiner

Shin-Lin Chen

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --
Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 11 September 2006.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-49 is/are pending in the application.
- 4a) Of the above claim(s) 1-9, 27-34 and 40-49 is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 10-26 and 35-39 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☒ The specification is objected to by the Examiner.
- 10) ☒ The drawing(s) filed on 11 March 2004 is/are: a) ☒ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- * See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- 1) ☒ Notice of References Cited (PTO-892)
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 3) ☒ Information Disclosure Statement(s) (PTO/SB/08)
Paper No(s)/Mail Date 5-26-04, 11-10-05, 3-9-06.
- 4) ☐ Interview Summary (PTO-413)
Paper No(s)/Mail Date. _____.
- 5) ☐ Notice of Informal Patent Application
- 6) ☐ Other: _____.

DETAILED ACTION

1. Applicant's election without traverse of group II, claims 10-26 and 35-39, in the reply filed on 9-11-06 is acknowledged.
2. Claims 1-9, 27-34 and 40-49 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim. Election was made **without** traverse in the reply filed on 9-11-06.

Applicant's preliminary amendment filed 9-11-06 has been entered. Claims 1-49 are pending. Claims 10-26 and 35-39 are under consideration.

Specification

3. The disclosure is objected to because of the following informalities: There is no "I claim:" or "What is claimed is:" on page 44 of the specification, which is the first page of the claims.

Appropriate correction is required.

Double Patenting

4. Applicant is advised that should claim 12 be found allowable, claim 16 will be objected to under 37 CFR 1.75 as being a substantial duplicate thereof. When two claims in an application are duplicates or else are so close in content that they both cover the same thing, despite a slight difference in wording, it is proper after allowing one claim to object to the other as being a substantial duplicate of the allowed claim. See MPEP § 706.03(k).

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5. Applicant is advised that should claim 21 be found allowable, claim 25 will be objected to under 37 CFR 1.75 as being a substantial duplicate thereof. When two claims in an application are duplicates or else are so close in content that they both cover the same thing, despite a slight difference in wording, it is proper after allowing one claim to object to the other as being a substantial duplicate of the allowed claim. See MPEP § 706.03(k).

Claim Rejections - 35 USC § 101

6. 35 U.S.C. 101 reads as follows:

Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

Claims 19-25 are rejected under 35 U.S.C. 101 because the claimed invention is directed to non-statutory subject matter. The claims encompass human beings, which are not considered patentable subject matter. See MPEP 2105. This rejection could be overcome by amending the claims to recite a “non-human transgenic animal”.

Claim Rejections - 35 USC § 112

7. The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

8. Claims 10-26, 36 and 38 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

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The phrase “capable of” in claims 10, 11, 18-20, 36 and 38 is vague and renders the claims indefinite. It is unclear as to the metes and bounds of what would be considered “capable of”. It is unclear to what extent is considered “capable of”. The specification fails to define the phrase “capable of”. Claims 12-14 depend from claim 11. Claims 15-17 depend from claim 10. Claims 21-26 depend from claim 19.

Claim Rejections - 35 USC § 101

9. 35 U.S.C. 101 reads as follows:

Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

Claim Rejections - 35 USC § 112

10. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

11. Claims 10-26 and 35-39 are rejected under 35 U.S.C. 101 because the claimed invention is not supported by either a specific and substantial asserted utility or a well-established utility.

Claims 10-26 and 35-38 are directed to a transgenic rabbit or animal comprising in its genome at least one stably incorporated expression cassette comprising (1) a promoter having the nucleotide sequence of SEQ ID No. 1 or 2, or having a sequence at least 90% identical to SEQ ID No. 1 or 2 or having a sequence comprising at least 50 contiguous nucleotides of SEQ ID No. 1 or 2, and (2) a heterologous nucleotide sequence operably linked to said promoter. Claims 11-14, 16, 20-23 and 25 specify the promoter initiates tissue-specific transcription, such as cardiac-specific, ventricle-specific, or atria-specific transcription. Claims 15 and 24 specify the rabbit or

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animal exhibit altered expression of the heterologous nucleotide sequence. Claim 17 specifies the heterologous nucleotide sequence comprises a nucleotide sequence of SEQ ID No. 3 encoding alpha-myosin heavy chain, a sequence having at least 95% identity to SEQ ID No. 3, or a sequence encoding the amino acid sequence of SEQ ID No. 4 or encoding an amino acid sequence at least 95% identical to SEQ ID No. 4. Claim 18 specifies the rabbit exhibits altered myosin isoform expression. Claim 39 is directed to a transgenic rabbit comprising in its genome at least one stably incorporated expression cassette comprising the nucleotide sequence of SEQ ID No. 5 (alpha-myosin heavy chain coding sequence operably linked to beta-myosin heavy chain promoter).

The specification discloses nucleotide sequences of SEQ ID Nos. 1-5 where SEQ ID Nos. 1 and 2 are alpha- and beta-myosin heavy chain promoters, respectively, SEQ ID Nos. 3 and 4 are coding sequence of alpha- and beta-myosin heavy chain, respectively, and SEQ ID No. 5 contains alpha-myosin heavy chain coding sequence operably linked to beta-myosin heavy chain promoter. The specification discloses generation of a transgenic rabbit comprising the sequence of SEQ ID No. 5 and transgenic rabbit line expressing CAT reporter gene under the control of beta-myosin heavy chain promoter (SEQ ID No. 2) (e.g. example 1 and 2), and transgenic ventricle tissue contains both alpha and beta myosin heavy chain isoform (example 6). The specification asserts that the transgenic rabbit or animal can be used in studying heart disease and conditions, in studying familial hypertrophic cardiomyopathies (e.g. [0007]) and for identifying anti-cardiopathic compounds by monitoring cardiopathic phenotype of the transgenic rabbit (e.g. [0010]).

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The asserted utility for the claimed transgenic rabbit or animal does not appear to be specific and substantial because the evidence of record has not provided any suggestion of a correlation between any phenotype of the claimed transgenic animals or rabbit, the altered myosin isoform expression, and a disease or a disorder. The specification fails to provide a correlation between the altered myosin isoform expression and any phenotype, if any, of the claimed transgenic animals or rabbit or a correlation between the phenotype, if any, of the claimed transgenic animals or rabbit and any disease or disorder, such as familial hypertrophic cardiomyopathies. No phenotype, such as a cardiopathic phenotype, has been disclosed for the claimed transgenic rabbit or transgenic animal. The asserted utility for the claimed transgenic rabbit or animal for studying heart disease and conditions, for studying familial hypertrophic cardiomyopathies or for identifying anti-cardiopathic compounds by monitoring cardiopathic phenotype of the transgenic rabbit does not appear to be specific and substantial because no phenotype has been disclosed for the claimed transgenic rabbit or animal and no correlation between a phenotype, if any, and a particular disease or disorder has been established. The specification essentially gives an invitation to experiment wherein the artisan is invited to elaborate a functional use for the transgenic animals or rabbit embraced by the claims. Therefore, the utility for studying heart disease and conditions, for studying familial hypertrophic cardiomyopathies or for identifying anti-cardiopathic compounds by monitoring cardiopathic phenotype of the transgenic rabbit is not apparent.

The specification fails to disclose any phenotype of the claimed transgenic animal or transgenic rabbit. Marian et al., 1999 (The Journal of Clinical Investigation, Vol. 104, No. 12, p. 1683-1692, IDS) generates transgenic rabbit containing a transgene construct comprising a

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human beta-myosin heavy chain cDNA under the control of murine beta-myosin heavy chain promoter (e.g. Figure 1), and the wild-type transgenic rabbit exhibited no gross or microscopic phenotype of heterotrophic cardiomyopathy (HCM). “The expression level of the wild-type transgenic protein was higher than that of the endogenous beta-MyHC protein in the heart, but the total MyHC protein pool remained unchanged, which indicates substitution of the endogenous protein by the transgene protein ... we did not observed any histological features of the HCM phenotype or echocardiographic abnormalities in the wild-type transgenic rabbits ... expression of wild-type human beta-MyHC in adult feline cardiac myocytes did not induce a phenotype (e.g. p. 1690, left column). It appears the state of the art shows that no phenotype has been observed in either transgenic rabbit or transgenic feline expressing wild-type human beta-MyHC. A transgenic animal or transgenic rabbit having no phenotype is indistinguishable from a wild-type animal or rabbit and does not have a specific and substantial utility or a well-established utility because one skilled in the art would not know where and what to look for in using said transgenic animal or rabbit. A substantial utility is a utility that defines a “real world” use. Utilities that require or constitute carrying out further research to identify or reasonably confirm a “real world” context of use are not substantial utilities. Absent the phenotype of the claimed transgenic animal or rabbit and the correlation between a phenotype of the claimed transgenic animal or rabbit and a particular disease or disorder, no “real world” use of the claimed transgenic animal or rabbit has been established. Therefore, the claimed transgenic animal or rabbit lacks a specific and substantial or a well-established utility.

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In light of the above, the skilled artisan would not find the asserted utility of the transgenic animals or rabbit encompassed by the claims to be specific and substantial or well established.

Claims 10-26 and 35-39 are also rejected under 35 U.S.C. 112, first paragraph. Specifically, since the claimed invention is not supported by either a specific and substantial asserted utility or a well established utility for the reasons set forth above, one skilled in the art clearly would not know how to use the claimed invention.

Claim Rejections - 35 USC § 112

12. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

13. Claims 10-26 and 35-38 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The claims read on numerous transgenic animals, such as mice, rats, sheep, pigs, canine, feline, monkeys, baboons, chimpanzees, whales, birds, insects, fishes etc., or transgenic rabbit expressing any heterologous polypeptide under the control of the promoter sequence of SEQ ID No. 1 or 2 or its variants, and transgenic rabbit expressing alpha or beta myosin heavy chain protein or its structural variants under the control of the promoter sequence of SEQ ID No. 1 or 2

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or its variants. The claims encompass numerous transgenic animals and rabbits having various unknown and unidentified phenotypes or having no phenotype. The specification fails to disclose any phenotype of the claimed transgenic animals or rabbits. The phenotypes of various transgenic animals or transgenic rabbits expressing any heterologous polypeptide, such as alpha or beta myosin heavy chain, under the control of the promoter sequence of SEQ ID No. 1 or 2 or its variants were unpredictable at the time of the invention as discussed below. The structural features and phenotypes of the transgenic animals or rabbits that can distinguish said transgenic animals or rabbits from corresponding wild-type animals or rabbits have not been disclosed. The general knowledge and level of skill in the art do not supplement the omitted description because specific, not general, guidance is what is needed. Since the disclosure fails to describe common attributes or characteristics that identify the claimed transgenic animals or rabbits, and because the claimed transgenic animals or rabbits are highly variant, the disclosure in the present application is insufficient to describe the claimed transgenic animals and rabbits.

This limited information is not sufficient to reasonably convey to one skilled in the art that applicants were in possession of the claimed transgenic animals and rabbits. Thus, it is concluded that the written description requirement is not satisfied for the transgenic animals and rabbits as claimed.

14. Claims 10-26 and 35-39 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

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Claims 10-26 and 35-38 are directed to a transgenic rabbit or animal comprising in its genome at least one stably incorporated expression cassette comprising (1) a promoter having the nucleotide sequence of SEQ ID No. 1 or 2, or having a sequence at least 90% identical to SEQ ID No. 1 or 2 or having a sequence comprising at least 50 contiguous nucleotides of SEQ ID No. 1 or 2, and (2) a heterologous nucleotide sequence operably linked to said promoter. Claims 11-14, 16, 20-23 and 25 specify the promoter initiates tissue-specific transcription, such as cardiac-specific, ventricle-specific, or atria-specific transcription. Claims 15 and 24 specify the rabbit or animal exhibit altered expression of the heterologous nucleotide sequence. Claim 17 specifies the heterologous nucleotide sequence comprises a nucleotide sequence of SEQ ID No. 3 encoding alpha-myosin heavy chain, a sequence having at least 95% identity to SEQ ID No. 3, or a sequence encoding the amino acid sequence of SEQ ID No. 4 or encoding an amino acid sequence at least 95% identical to SEQ ID No. 4. Claim 18 specifies the rabbit exhibits altered myosin isoform expression. Claim 39 is directed to a transgenic rabbit comprising in its genome at least one stably incorporated expression cassette comprising the nucleotide sequence of SEQ ID No. 5 (alpha-myosin heavy chain coding sequence operably linked to beta-myosin heavy chain promoter).

The specification discloses nucleotide sequences of SEQ ID Nos. 1-5 where SEQ ID Nos. 1 and 2 are alpha- and beta-myosin heavy chain promoters, respectively, SEQ ID Nos. 3 and 4 are coding sequence of alpha- and beta-myosin heavy chain, respectively, and SEQ ID No. 5 contains alpha-myosin heavy chain coding sequence operably linked to beta-myosin heavy chain promoter. The specification discloses generation of a transgenic rabbit comprising the sequence of SEQ ID No. 5 and transgenic rabbit line expressing CAT reporter gene under the control of

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beta-myosin heavy chain promoter (SEQ ID No. 2) (e.g. example 1 and 2), and transgenic ventricle tissue contains both alpha and beta myosin heavy chain isoform (example 6).

The claims read on numerous transgenic animals, such as mice, rats, sheep, pigs, canine, feline, monkeys, baboons, chimpanzees, whales, birds, insects, fishes etc., or transgenic rabbit expressing any heterologous polypeptide under the control of the promoter sequence of SEQ ID No. 1 or 2 or its variants, and transgenic rabbit expressing alpha or beta myosin heavy chain protein or its structural variants under the control of the promoter sequence of SEQ ID No. 1 or 2 or its variants. The claims encompass numerous transgenic animals and rabbits having various unknown and unidentified phenotypes or having no phenotype.

The specification fails to provide adequate guidance and evidence for how to make the claimed transgenic animals or rabbits. The specification also fails to disclose any phenotype of the claimed transgenic animals or transgenic rabbits. A transgenic animal or transgenic rabbits having no phenotype is indistinguishable from a wild-type animal or rabbit and one skilled in the art at the time of the invention would not know how to use the claimed transgenic animals or rabbits.

The level of one of ordinary skill in the art is high regarding making transgenic animal or rabbit. The art of transgenics at the time of the invention held that the resulting phenotype of a transgenic animal or mouse was unpredictable at the time of the invention. Kappel et al., 1992 (Current Opinion in Biotechnology, Vol. 3, p. 548-553) reports that the individual gene of interest, promoter, enhancer, coding or non-coding sequences present in the transgene construct, the site of integration, etc., are the important factors that governs the expression of a transgene (e.g. p. 549)). Wall, R. J., 1996 (Theriogenology, Vol. 45, p. 45-68) states that “[o]ur lack of

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understanding of essential genetic control elements makes it difficult to design transgenes with predictable behavior” (e.g. p. 61, last paragraph), and “transgene expression and the physiological consequences of transgene products in livestock are not always accurately predicted in transgenic mouse studies” (e.g. p. 62, first paragraph). Strojek et al., 1988 (Genetic Engineering: Principles and Methods, Vol. 10, pp. 221-246) points out that “genetic and species-specific conditions can cause different limitations or gene integration efficiency” and “transgenic mouse work alone is only of limited value when problems arising in the production of transgenic livestock are to be solved, particularly when there is a necessity of finding cis-acting factors which are suitable for appropriate gene expression in a given species” (e.g. p. 238-239).

Further, the genetic background of the transgenic mice has a large impact on the resulting phenotype of the transgenic animals or mice. Sigmund, C., June 2000 (Arterioscler. Thromb. Vasc. Biol., p. 1425-1429), reports that variation in the genetic background contributes to unpredictable resulting phenotypes of transgenic or gene-targeted animals. “Animals containing the same exact genetic manipulation exhibit profoundly different phenotypes when present on diverse genetic backgrounds, demonstrating that genes unrelated, per se, to the ones being targeted can play a significant role in the observed phenotype” (e.g. abstract). Sigmund further states that “many of the phenotypes examined in transgenic and knockout models are influenced by the genetic background in which they are studied...Although all mouse strains contain the same collection of genes, it is allelic variation...and the interaction between allelic variants that influence a particular phenotype. These “epigenetic” effects can dramatically alter the observed phenotype and therefore can influence or alter the conclusions drawn from experiments” (e.g. introduction). Mogil et al., 1999 (Pain, Vol. 80, pages 67-82) reports that there are several

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limitations to the use of mouse transgenic KO models. Mogil teaches that “the embryonic stem (ES) cell lines used to carry the targeted mutation are all derived from various substrains of the 129 strain” and “it is difficult to separate by homologous recombination the 129-derived transgene from tightly linked gene. Even after repeated backcrosses to C57Bl/6, a step most often omitted in the competition to publish, the wild-type and KO populations will differ in their inheritance of so-called “hitchhiking donor gene” alleles”. Knockout mutant mice will inherit alleles tightly linked with the gene disruption, leading to “hitchhiking donor gene” alleles from 129 ES cell lines while the wild-type mice will inherit C57BL/6-derived alleles. “[O]bserved phenotypic differences between wild-type and KO mice could, therefore, be due to the targeted mutation, to allelic variation at one or more of the many unidentified hitchhiking genes, or to an interaction between them” (page 78, left column). In addition, “the background genes from the parent strains can interact with the targeted mutation (“epistasis”), importantly affecting the observed phenotype” (page 78, left column).

In addition, Houdebine, L-M., 2002 (Journal of Biotechnology, Vol. 98, p. 145-160) points out that reintegration of an isolated gene into the genome of an animal by gene microinjection may generate complex and unpredictable biological situations (e.g. p. 146, first paragraph). Houdebine states that “animal transgenics is still suffering from technical limitations” (e.g. abstract). Mercier et al., 1997 (“The modification of milk protein composition through transgenesis: progress and problems,” In: Transgenic Animals: Generation and use, Ed. Houdebine LM, Harwood Academic Publishers, The Netherlands pp: 473-482) teach that “much progress remains to be done before routinely using transgenesis for generating farm animals producing milk for non-therapeutic use. In the present state of the art, it is difficult to predict

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that a construct will be functional because of insufficient knowledge on gene transcript, Pre-mRNA processing, RNA and protein stability. Integration of the microinjected transgene is aleatory resulting in highly variable levels of expression, and possible detrimental effects." (e.g. p. 479, right column). It appears that the individual gene of interest, promoter used, enhancer, coding or non-coding sequences present in the transgene construct, the site of integration, and the genetic background of the transgenic animal determine the expression level of the desired gene product and the resulting phenotype of the transgenic animals or rabbits.

Further, it was known in the art the transcriptional activity of a promoter was unpredictable from mere the nucleotide sequence of a promoter. A slight change of a promoter sequence could result in dramatically increase or decrease in the transcriptional activity of said promoter. Variants of promoter sequence SEQ ID No. 1 or 2 could also have dramatically different transcriptional activity as compared to the promoter sequence of SEQ ID No. 1 or 2.

It was also known in the art that the amino acid sequence of a polypeptide determines its structural and functional properties (including half-life), and predictability of which amino acid(s) can be removed from or added to a polypeptide's sequence and still result in similar activity or result in stabilization of the protein is extremely complex, and well outside the realm of routine experimentation. Rudinger, 1976 (Peptide Hormones, Parsons, University Park Press, Baltimore, p. 1-7) points out that "The significance of particular amino acids and sequences for different aspects of biological activity cannot be predicted *a priori* but must be determined from case to case by painstaking experimental study" (e.g. p. 6). Kaye et al., 1990 (Proc. Natl. Acad. Sci. USA, Vol. 87, pp. 6922-6926) discloses that a single amino acid substitution results in a retinoblastoma protein defective in phosphorylation and oncoprotein binding (e.g. title). In

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addition, Skolnick et al., 2000 (Trends in Biotech, Vol. 18, p. 34-39) states “Sequence-based methods for function prediction are inadequate because of the multifunctional nature of proteins. However, just knowing the structure of the protein is also insufficient for prediction of multiple functional sites. Structural descriptors for protein functional sites are crucial for unlocking the secrets in both the sequence and structural-genomics projects” (e.g. abstract). Skolnick further states that “Knowing a protein’s structure does not necessarily tell you its function” and “Because proteins can have similar folds but different functions, determining the structure of a protein may or may not tell you something about its function” (e.g. p. 36, box 2). Therefore, biological function of a protein was unpredictable from mere amino acid sequence at the time of the invention. The unpredictable promoter activity of different promoter sequences and the unpredictable biological function of different proteins at the time of the invention add to the unpredictability of the resulting phenotype of the claimed transgenic animals and rabbits of the instant invention.

In view of the unpredictable promoter activity and biological function of a protein, the inherent unpredictability of the resulting phenotypes of transgenic animals or rabbits and the lack of any phenotype of the claimed transgenic animals or rabbits, one skilled in the art at the time of the invention would not know how to use the claimed transgenic animals or rabbits. For the reasons set forth above, one skilled in the art at the time of the invention would have to engage in undue experimentation to practice over the full scope of the invention claimed. This is particularly true based upon the nature of the claimed invention, the state of the art, the unpredictability found in the art, the teaching and working examples provided, the level of one of

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ordinary skill which is high, the amount of experimentation required, and the breadth of the claims.

Claim Rejections - 35 USC § 102

15. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

Claim Rejections - 35 USC § 103

16. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

17. Claims 10-13, 15, 16, 19-22 and 24-26 are rejected under 35 U.S.C. 102(b) as anticipated by or, in the alternative, under 35 U.S.C. 103(a) as obvious over Marian et al., 1999 (The Journal of Clinical Investigation, Vol. 104, No. 12, p. 1683-1692, IDS).

Claims 10-13, 15, 16, 19-22 and 24-26 are directed to a transgenic rabbit or animal comprising in its genome at least one stably incorporated expression cassette comprising (1) a promoter having the nucleotide sequence of SEQ ID No. 1 or 2, or having a sequence at least 90% identical to SEQ ID No. 1 or 2 or having a sequence comprising at least 50 contiguous nucleotides of SEQ ID No. 1 or 2, and (2) a heterologous nucleotide sequence operably linked to said promoter. Claims 11-13, 16, 20-22 and 25 specify the promoter initiates tissue-specific

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transcription, such as cardiac-specific, or ventricle-specific transcription. Claims 15 and 24 specify the rabbit or animal exhibit altered expression of the heterologous nucleotide sequence.

Marian generates transgenic rabbit containing a transgene construct comprising a human beta-myosin heavy chain cDNA under the control of 7kb murine beta-myosin heavy chain promoter (e.g. Figure 1), and the wild-type transgenic rabbit exhibited no gross or microscopic phenotype of heterotrophic cardiomyopathy (HCM). "The expression level of the wild-type transgenic protein was higher than that of the endogenous beta-MyHC protein in the heart, but the total MyHC protein pool remained unchanged, which indicates substitution of the endogenous protein by the transgene protein ... we did not observed any histological features of the HCM phenotype or echocardiographic abnormalities in the wild-type transgenic rabbits ... expression of wild-type human beta-MyHC in adult feline cardiac myocytes did not induce a phenotype (e.g. p. 1690, left column). It is very likely that the 7kb murine beta-myosin heavy chain promoter has at least 50 contiguous nucleotides of SEQ ID No. 1 or 2, therefore, the claims are anticipated by Marian. If the 7kb murine beta-myosin heavy chain promoter does not have at least 50 contiguous nucleotides of SEQ ID No. 1 or 2, it would have been obvious for one of ordinary skill in the art to make the claimed transgenic rabbit according to the teaching of Marian because Marian teaches making a transgenic rabbit expressing a wild-type beta-myosin heavy chain protein under the control of a beta-myosin heavy chain promoter and no phenotype is needed in the claimed transgenic animal or rabbit.

Claim Rejections - 35 USC § 102

18. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

19. Claims 10-26 are rejected under 35 U.S.C. 102(b) as being anticipated by James et al., 2000 (Circulation, Vol. 101, p. 1715-1721, IDS).

Claims 10-26 are directed to a transgenic rabbit or animal comprising in its genome at least one stably incorporated expression cassette comprising (1) a promoter having the nucleotide sequence of SEQ ID No. 1 or 2, or having a sequence at least 90% identical to SEQ ID No. 1 or 2 or having a sequence comprising at least 50 contiguous nucleotides of SEQ ID No. 1 or 2, and (2) a heterologous nucleotide sequence operably linked to said promoter. Claims 11-14, 16, 20-23 and 25 specify the promoter initiates tissue-specific transcription, such as cardiac-specific, ventricle-specific, or atria-specific transcription. Claims 15 and 24 specify the rabbit or animal exhibit altered expression of the heterologous nucleotide sequence. Claim 17 specifies the heterologous nucleotide sequence comprises a nucleotide sequence of SEQ ID No. 3 encoding alpha-myosin heavy chain, a sequence having at least 95% identity to SEQ ID No. 3, or a sequence encoding the amino acid sequence of SEQ ID No. 4 or encoding an amino acid sequence at least 95% identical to SEQ ID No. 4. Claim 18 specifies the rabbit exhibits altered myosin isoform expression.

James teaches making transgenic rabbits by using expression construct comprising the mouse alpha or beta myosin heavy chain (MHC) promoter operably linked to nucleotide

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sequence encoding CAT and show that both MHC promoter drive high levels of transgene expression in the cardiac compartment in rabbit but not active in smooth muscle or nonmuscle tissues (e.g. abstract). Both the mouse alpha-MHC and beta-MHC promoters are about 85% identical with the respective rabbit promoters in the proximal 600 bp (e.g. p. 1716, left column). The mouse alpha-MHC and beta-MHC promoters would comprise at least 50 contiguous nucleotide sequence of SEQ ID No. 1 and 2, respectively. CAT reporter gene is a heterologous nucleotide sequence. Thus, claims 10-26 are anticipated by James.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Shin-Lin Chen whose telephone number is (571) 272-0726. The examiner can normally be reached on Monday to Friday from 9:30 am to 6 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram Shukla can be reached on (571) 272-0735. The fax phone number for this group is (571) 273-8300.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

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Shin-Lin Chen, Ph.D.

A handwritten signature in black ink, appearing to read 'S Chen', is positioned above the printed name.

**SHIN-LIN CHEN
PRIMARY EXAMINER**